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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

Trost and Hachiya

SERIAL NO.: 09/498,701

FILED: February 7, 2000

FOR: **CATALYTIC COMPOSITIONS AND METHODS FOR ASYMMETRIC ALLYLIC ALKYLATION**

EXAMINER: A.L. Rotman

ART UNIT: 1625

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

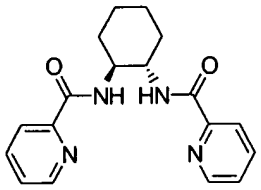
I, Barry M. Trost, declare and affirm as follows:

I received a Ph.D. from the Massachusetts Institute of Technology in 1965. I currently hold the position of Professor of Chemistry at Stanford University, which I have held since 1987. I have authored and coauthored numerous monographs and articles in the field of synthetic organic chemistry.

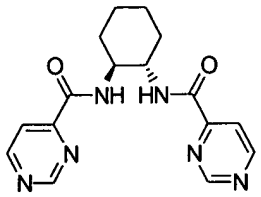
I am a coinventor in the above-referenced application.

I supervised, participated in, and/or have firsthand knowledge of the studies reported below.

The above-referenced application describes and claims methods and catalysts for use in asymmetric allylic alkylation reactions. Preferred catalysts are molybdenum complexes of chiral ligands which include heterocyclic binding components, as disclosed in the application. Data were presented in the application for reactions employing chiral ligands in which the heterocyclic binding components were variously substituted pyridines or 2-quinoline. The results described below show the effectiveness of additional nitrogen heterocycles as binding groups in the subject reactions.



I



II

In ligand **II**, the pyridine rings of ligand **I** are replaced by pyrimidine rings. Reactions employing this ligand were run in accordance with the general procedure. (Active catalyst was generated by heating a solution of $Mo(CO)_3(EtCN)_3$ and ligand; a solution of sodiomalonate and substrate was added dropwise via syringe at about 60°C, and the mixture was heated at 85-90°C, as indicated, for 2 hours.) Results are shown in Table 1.

Reactions using ligand **II** gave similar branched-to-linear product ratios as obtained with ligand **I**. However, yields were improved, and the reaction time was greatly reduced (Table 1). For substrate **9** (entry 4), enantioselectivity was also increased over that obtained with ligand **I**.

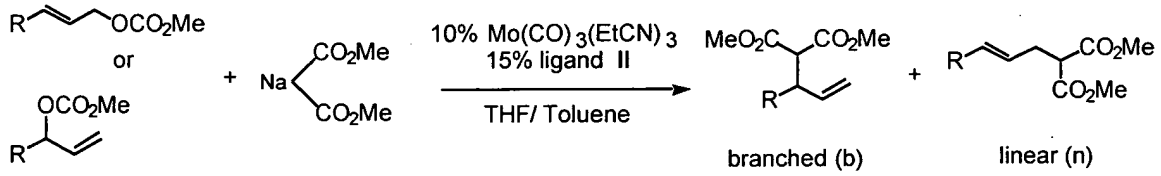
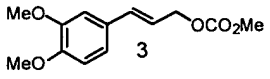
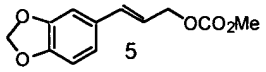
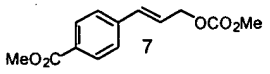
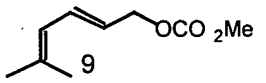
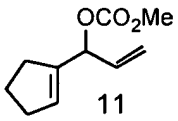
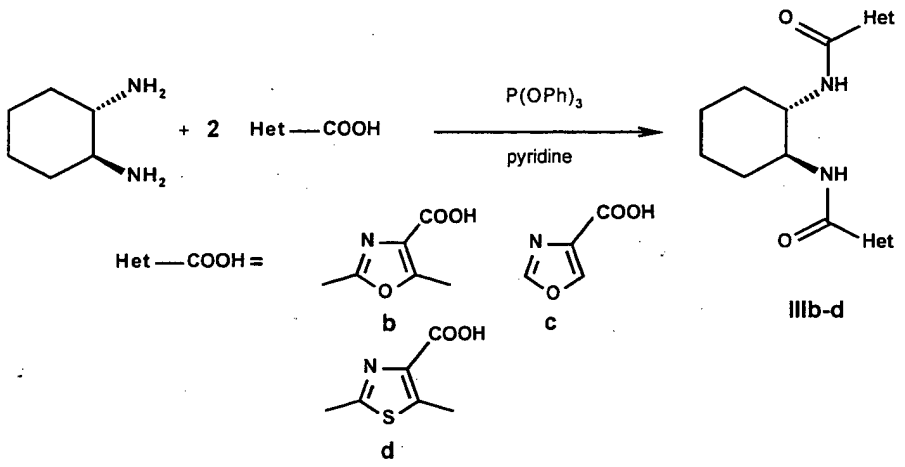


Table 1

entry	substrate	temp (°C)	yield (%)	ratio (b/n)	ee (%)
1	 3	85	81.5	92/8	99
2	 5	85	93.6	94/6	99
3	 7	85	84	87/13	99
4	 9	90	94	94/6	91
5	 11	90	88	93/7	86

Ligands having various 5-membered heterocyclic rings were prepared by the general method shown below. The designation "Het—COOH" represents, respectively, 2,5-dimethyloxazole-4-carboxylic acid (used to make ligand **IIIb**), oxazole-4-carboxylic acid (used to make ligand **IIIc**), and 2,5-dimethylthiazole-4-carboxylic acid (used to make ligand **IIId**), as shown.



Reactions were run using the following general procedure. Catalyst was generated by heating a solution of 0.05 mmol of the Mo complex $C_7H_8Mo(CO)_3$ and 0.075 mmol ligand in 1 ml of THF at 60°C for 20 min. Sodiomalonate (1.0 mmol; formed by reaction of the malonate with sodium tert-butylate) in 2 ml THF and 0.5 mmol substrate in 1 ml THF were added, and the mixture was stirred at the temperature indicated for 16 hrs. Results are shown in Table 2.

Yields, which were not optimized, were modest (possibly due to contamination and deactivation of the catalyst), but enantioselectivity was excellent. Very high regioselectivity was obtained with catalyst **IIId** at low temperature.

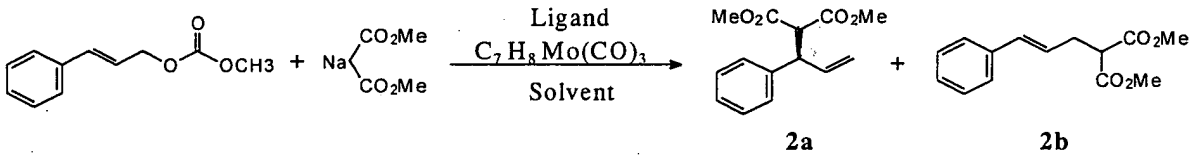


Table 2

ligand	temp (°C)	yield[a] (2a+2b)	ratio[b] (2a:2b)	ee[c] (%)
IIIb	25	55	33:1	99
IIIb	40	60	34:1	99
IIIc	60	23(36)	21:1	99
IIId	25	20(30)	100:1	99

a) Isolated Yields. Yields in parentheses are based upon recovered starting material.
b) Determined by ^{1}H NMR of the isolated product.
c) Determined by enantioselective HPLC or comparison with known values.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

3/23/01
Date

Barry M. Trost
Barry M. Trost, Ph.D.